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(54) COMPOSES DE REGULATION DES CANAUX IONIQUES ET UTILISATIONS DE CES PRODUITS
(54) ION CHANNEL MODULATING COMPOUNDS AND USES THEREOF

(57)

Ion channel modulating compounds are disclosed. The compounds of the present invention may be incorporated in compositions and kits. The present invention also discloses a variety of in vitro and in vivo uses for the compounds and compositions, including the treatment of arrhythmia and the production of analgesia and local anesthesia.

ION CHANNEL MODULATING COMPOUNDS AND USES THEREOF

ABSTRACT OF THE DISCLOSURE

Ion channel modulating compounds are disclosed. The compounds of the present invention may be incorporated in compositions and kits. The present invention also discloses a variety of *in vitro* and *in vivo* uses for the compounds and compositions, including the treatment of arrhythmia and the production of analgesia and local anesthesia.

123(1):264-7 Jan. 1992). Its prevalence is likely to increase as the population ages and it is estimated that 3-5% of patients over the age of 60 years have AF (Kannel W.B., Abbot R.D., Savage D.D., McNamara P.M., *N. Engl. J. Med.* 306(17):1018-22, 1982; Wolf P.A., Abbot R.D., Kannel W.B. *Stroke.* 22(8):983-8, 1991). While AF is rarely fatal, it can impair cardiac function and is a major cause of stroke (Hinton R.C., Kistler J.P., Fallon J.T., Friedlich A.L., Fisher C.M., *American Journal of Cardiology 40(4)*:509-13, 1977; Wolf P.A., Abbot R.D., Kannel W.B., *Archives of Internal Medicine 147(9)*:1561-4, 1987; Wolf P.A., Abbot R.D., Kannel W.B. *Stroke. 22(8)*:983-8, 1991; Cabin H.S., Clubb K.S., Hall C., Perlmutter R.A., Feinstein A.R., *American Journal of Cardiology 65(16)*:1112-6, 1990).

Antiarrhythmic agents have been developed to prevent or alleviate cardiac arrhythmia. For example, Class I antiarrhythmic compounds have been used to treat supraventricular arrhythmias and ventricular arrhythmias. Treatment of ventricular arrhythmia is very important since such an arrhythmia can be fatal. Serious ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) occur most often in the presence of myocardial ischemia and/or infarction. Ventricular fibrillation often occurs in the setting of acute myocardial ischemia, before infarction fully develops. At present, there is no satisfactory pharmacotherapy for the treatment and/or prevention of ventricular fibrillation during acute ischemia. In fact, many Class I antiarrhythmic compounds may actually increase mortality in patients who have had a myocardial infarction.

Class Ia, Ic and III antiarrhythmic drugs have been used to convert recent onset AF to sinus rhythm and prevent recurrence of the arrhythmia (Fuch and Podrid, 1992; Nattel S., Hadjis T., Talajic M., *Drugs 48(3)*:345-71, 1994). However, drug therapy is often limited by adverse effects, including the possibility of increased mortality, and inadequate efficacy (Feld G.K., *Circulation. 83(6)*:2248-50, 1990; Coplen S.E., Antman E.M., Berlin J.A., Hewitt P., Chalmers T.C., *Circulation* 1991; *83(2)*:714 and *Circulation 82(4)*:1106-16, 1990; Flaker G.C., Blackshear J.L., McBride R., Kronmal R.A., Halperin J.L., Hart R.G., *Journal of the American College of Cardiology 20(3)*:527-32, 1992; CAST, *N. Engl. J. Med.* 321:406, 1989; Nattel S.,

include, but are not limited to, the transient outward current I_{to1} such as Kv4.2 and Kv4.3), and the ultrarapid delayed rectifier current (I_{Kur}) such as Kv1.5, Kv1.4 and Kv2.1). The ultrarapid delayed rectifier current (I_{Kur}) has also been described as I_{sus}. A second calcium dependent transient outward current (I_{to2}) has also been described.

The cardiac pathological conditions that may be treated and/or prevented by the present invention may include, but are not limited to, arrhythmias such as the various types of atrial and ventricular arrhythmias.

In one embodiment, the present invention provides ion channel modulating compounds that can be used to selectively inhibit cardiac early repolarising currents and cardiac sodium currents.

In another embodiment, the present invention provides ion channel modulating compounds that can be used to selectively inhibit cardiac early repolarising currents and cardiac sodium currents under conditions where an "arrhythmogenic substrate" is present in the heart. An "arrhythmogenic substrate" is characterized by a reduction in cardiac action potential duration and/or changes in action potential morphology, premature action potentials, high heart rates and may also include increased variability in the time between action potentials and an increase in cardiac milieu acidity due to ischaemia or inflammation. Changes such as these are observed during conditions of myocardial ischaemia or inflammation and those conditions that precede the onset of arrhythmias such as atrial fibrillation.

In another embodiment, the present invention provides aminocyclohexyl ether compounds of formula (I), or a solvate or pharmaceutically acceptable salt thereof:

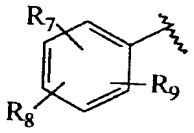
and any two adjacent additional carbon ring atoms may be fused to a C_3-C_8carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1-C_6alkyl, C_2-C_4acyl, C_2-C_4hydroxyalkyl and C_3-C_8alkoxyalkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]-hexan-3-yl and 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring shown in formula (I) at the 3-, 4-, 5- or 6- positions and are independently selected from hydrogen, hydroxy, C_1-C_6alkyl and C_1-C_6alkoxy, and, when both R_3 and R_4 are attached to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur;

R_5, R_6 and R_{14} are independently selected from hydrogen, C_1-C_6alkyl, aryl and benzyl, or R_6 and R_{14}, when taken together with the carbon to which they are attached, may form a spiro C_3-C_5cycloalkyl;

A is selected from C_5-C_{12}alkyl, a C_3-C_{13}carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII) and (VIII):



(III)

where R_7, R_8 and R_9 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, aryl and N(R_{15},R_{16}) where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl and C_1-C_6alkyl;

In other embodiments, the present invention provides a composition or medicament that includes a compound according to formula (I) in combination with a pharmaceutically acceptable carrier, diluent or excipient, and further provides a method for the manufacture of a composition or medicament that contains a compound according to formula (I).

In other embodiments, the present invention provides pharmaceutical compositions that contain at least one compound of formula (I) in an amount effective to treat a disease or condition in a warm-blooded animal suffering from or having the disease or condition, and/or prevent a disease or condition in a warm-blooded animal that would otherwise occur, and further contains at least one pharmaceutically acceptable carrier, diluent or excipient. The invention further provides for methods of treating a disease or condition in a warm-blooded animal suffering from or having the disease or condition, and/or preventing a disease or condition from arising in a warm-blooded animal, wherein a therapeutically effective amount of a compound of formula (I), or a composition containing a compound of formula (I) is administered to a warm-blooded animal in need thereof. The diseases and conditions to which the compounds, compositions and methods of the present invention have applicability are as follows: arrhythmia, diseases of the central nervous system, convulsion, epileptic spasms, depression, anxiety, schizophrenia, Parkinson's disease, respiratory disorders, cystic fibrosis, asthma, cough, inflammation, arthritis, allergies, gastrointestinal disorders, urinary incontinence, irritable bowel syndrome, cardiovascular diseases, cerebral or myocardial ischemias, hypertension, long-QT syndrome, stroke, migraine, ophthalmic diseases, diabetes mellitus, myopathies, Becker's myotonia, myasthenia gravis, paramyotonia congentia, malignant hyperthermia, hyperkalemic periodic paralysis, Thomsen's myotonia, autoimmune disorders, graft rejection in organ transplantation or bone marrow transplantation, heart failure, hypotension, Alzheimer's disease or other metal disorder, and alopecia.

In another embodiment, the present invention provides a pharmaceutical composition containing an amount of a compound of formula (I) effective to produce local analgesia or anesthesia in a warm-blooded animal in need thereof, and a

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the reaction sequence further described in Example 1, for preparing an aminocyclohexyl ether compound of the present invention.

Figure 2 illustrates a procedure whereby either *cis*- or *trans*-aminocyclohexyl ether compounds of the present invention may be prepared.

Figure 3 illustrates synthetic methodology that may be employed to prepare either *cis* or *trans* stereoisomers of the compounds of the present invention.

Figures 4A and 4B illustrate the synthetic methodology described in Example 15.

DETAILED DESCRIPTION OF THE INVENTION

As briefly noted above, in one aspect the present invention provides for the treatment and/or prevention of a variety of cardiac pathological conditions by the use of one or more ion channel modulating compounds that either singly, or together with one or more additional compounds, are able to inhibit selective cardiac ionic currents. More specifically, the cardiac currents referred to above are the sodium currents and early repolarising currents.

Early repolarising currents correspond to those cardiac ionic currents which activate rapidly after depolarisation of membrane voltage and which effect repolarisation of the cell. Many of these currents are potassium currents and may include, but are not limited to, the transient outward current (I_{to1} such as Kv4.2 and Kv4.3), and the ultrarapid delayed rectifier current (I_{Kur} such as Kv1.5, Kv1.4, and Kv2.1). The ultrarapid delayed rectifier current (I_{Kur}) has also be described as I_{sus}. A second calcium dependent transient outward current (I_{to2}) has also been described.

The cardiac pathological conditions that may be treated and/or prevented by the novel methods of the present invention may include, but are not limited to, arrhythmias such as the various types of atrial (supraventricular) and ventricular arrhythmias. The compounds of the present invention are especially useful in treating and/or preventing atrial fibrillation and ventricular fibrillation.

currents and early repolarising currents. It is preferable that the ion channel modulating compounds block the said cardiac currents from extracellular loci. Such compounds act on an external locus of the ion channel that is accessible from the extracellular surface. This facilitates access to the ion channel and provides rapid onset kinetics and exhibits frequency dependent blockade of currents. Such properties are all beneficial for compounds used to treat arrhythmias.

The novel methods of the present invention provide treatment and/or prevention of arrhythmias that do not prolong action potential duration in normal cardiac ventricle but rather prolongs action potential duration under conditions when an arrhythmogenic substrate is present in the heart. Blockade of early, rather than late repolarising currents will prolong action potential duration under conditions where action potential duration has been *previously* reduced. Blockade of early, rather than late, repolarising currents offers another advantage over existing methods. Blockade of late repolarising currents such as I_{Kr} (HERG) and I_{Ks} (minK-LQT) prolongs action potential under normal conditions. In so doing there is a risk of precipitating a polymorphic ventricular tachycardia commonly called torsade de pointes which can be fatal (Nattel, 1998). As blockade of early repolarising currents does not prolong action potential duration under normal conditions, the novel methods of the present invention greatly reduce such proarrhythmia risk.

Methods for *in vitro* assessment of inhibition activity of ion channel modulating compounds on different cardiac ion currents are well known in the art and are briefly described in Example 33 below.

Methods for assessment of proarrhythmia (*e.g.*, torsade de pointes) risk of ion channel modulating compounds are also published in the literature and are briefly described in Example 34 below.

In the novel methods of the present invention of treating and/or preventing arrhythmia, one or more ion channel modulating compounds, either singly or together, are used to inhibit selective cardiac sodium currents and cardiac early repolarising currents. The concentration of each compound is typically between 0.001 and 30 μM.

prevention, and (b) a pharmaceutically acceptable carrier, diluent, or excipient. According to the present invention, this composition may be used in a method for treating or preventing atrial arrhythmia in a warm-blooded animal, where the method comprises administering to a warm-blooded animal in need thereof a therapeutically effective amount of one of the above-described ion channel modulating compounds or a composition containing same.

The invention further provides a pharmaceutical composition comprising (a) an amount of an ion channel modulating compound as described above effective to treat or prevent ventricular arrhythmia in a warm-blooded animal in need of the treatment or prevention, and (b) a pharmaceutically acceptable carrier, diluent, or excipient. This composition may be used in a method for treating or preventing ventricular arrhythmia in a warm-blooded animal, where the method comprises administering to a warm-blooded animal in need thereof a therapeutically effective amount of one of the above-described ion channel modulating compounds or a composition containing same.

The invention further provides a method for inhibiting multiple cardiac ionic current, where the method comprises administering to a warm-blooded animal in need thereof one or more compounds that either singly or together both block cardiac early repolarising currents and cardiac sodium currents, said one or more compounds being administered in an amount effective to block cardiac sodium currents and cardiac early repolarising currents. In this method, said one or more compounds may either singly or together both block cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

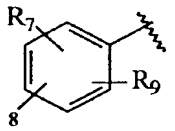
The present invention also provides a method for inhibiting multiple cardiac ionic currents, where the method comprises administering to a warm-blooded animal in need thereof one or more compounds that either singly or together both block the cardiac ion channels responsible for early repolarising currents and sodium channels, said one or more compounds being administered in an amount effective to block the cardiac sodium ion channels and the cardiac early repolarising ion channels. In this method, said one or more compounds may either singly or together both block

pH of the cardiac milieu, where the method comprises administering to a warm-blooded animal in need thereof, in an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac early repolarising currents and cardiac sodium currents. In this method, said one or more compounds may either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells. Also in this method, one compound may block cardiac ion channels responsible for early repolarising currents and in addition block sodium currents from extracellular loci in cardiac cells. In this method, each of said one or more compounds may have a pKa value of less than 8.

The present invention also provides a method for treating or preventing a cardiac condition wherein there is an increase in acidity from the normal physiological pH of the cardiac milieu, where the method comprises administering to a warm-blooded animal in need thereof, in an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents. In this method, said one or more compounds may either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells. Also in this method, one compound may both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells. Additionally, in this method, each of said one or more compounds may have a pKa value of less than 8.

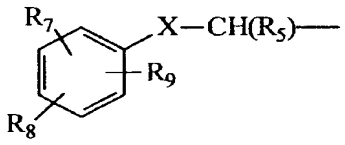
In a preferred embodiment, in the above-described methods, the cardiac condition is ventricular arrhythmia. In another preferred embodiment, in the above-described methods, the cardiac condition is atrial arrhythmia. In some instances, the increase in acidity of the cardiac milieu is due to myocardial ischaemia. Additionally, or alternatively, the increase in acidity of the cardiac milieu is due to high heart rate. Additionally, or alternatively, the increase in acidity is due to inflammation. Additionally, or alternatively, the increase in acidity is due to the presence of an

intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position. For example, compounds of the invention containing the A-X-CH(R_5)- group where A equals formula (III)



(III)

are intended to encompass compounds having the group (B):



(B)

where the group (B) is intended to encompass groups wherein any ring atom that could otherwise be substituted with hydrogen, may instead be substituted with either R_7, R_8 or R_9, with the proviso that each of R_7, R_8 and R_9 appears once and only once on the ring. Ring atoms that are not substituted with any of R_7, R_8 or R_9 are substituted with hydrogen. In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be present at different atoms of the ring, or on the same atom of the ring, so long as that atom could otherwise be substituted with a hydrogen atom.

Likewise, where the invention specifies compounds containing the A-X-CH(R_5)- group where A equals the aryl group (VI)

The phrase "independently at each occurrence" is intended to mean (i) when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (*e.g.*, R_1 within the set R_1 and R_2) is selected without regard the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In accordance with the present invention and as used herein, the following terms are defined to have following meanings, unless explicitly stated otherwise:

"Acid addition salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

"Acyl" refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl -(C=O)- group containing the specified number of carbon atoms. Examples include acetyl [CH_3C=O-, a C_2acyl] and propionyl [CH_3CH_2C=O-, a C_3acyl].

"Alkanoyloxy" refers to an ester substituent wherein the ether oxygen is the point of attachment to the molecule. Examples include propanoyloxy [(CH_3CH_2C=O-O-, a C_3alkanoyloxy] and ethanoyloxy [CH_3C=O-O-, a C_2alkanoyloxy].

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example, methoxy [-OCH_3, a C_1alkoxy].

"Alkoxyalkyl" refers to a alkylene group substituted with an alkoxy group. For example, methoxyethyl [$CH_3OCH_2CH_2$-] and ethoxymethyl ($CH_3CH_2OCH_2$-] are both C_3alkoxyalkyl groups.

"Carbocyclic aryl" refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

"Heteroatom" refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present invention.

"Heteroaryl" refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in "Handbook of Chemistry and Physics," 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

"Hydroxyalkyl" refers to a branched or unbranched hydrocarbon fragment bearing an hydroxy (-OH) group. Examples include hydroxymethyl ($-CH_2OH$, a C_1hydroxyalkyl) and 1-hydroxyethyl ($-CHOHCH_3$, a C_2hydroxyalkyl).

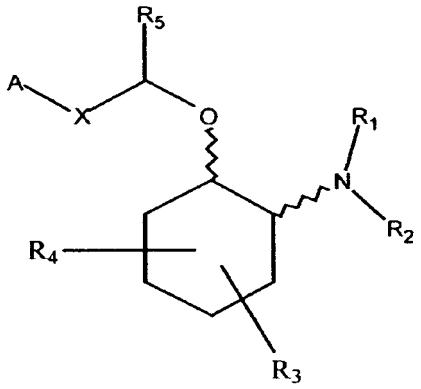
"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH_3S-, a C_1thioalkyl).

"Modulating" in connection with the activity of an ion channel means that the activity of the ion channel may be either increased or decreased in response to administration of a compound or composition or method of the present invention. Thus, the ion channel may be activated, so as to transport more ions, or may be blocked, so that fewer or no ions are transported by the channel.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the

Compounds of the Present Invention

The compounds of the present invention are amines which may be represented by formula (I):



(I)

Compounds of formula (I) are aminocyclohexyl ethers. More specifically, these aminocyclohexyl ethers are substituted at position 2 of the cyclohexyl ring with an amine group $-NR_1R_2$. The cyclohexyl ring may also be substituted with additional substituents (designated as R_3 and R_4) as described in more detail below. Examples of specific embodiments of compounds represented by formula (I) are described below

Depending upon the selection of substituents R_1 and R_2, the compounds of formula (I) may be primary, secondary, or tertiary amines (*i.e.*, both R_1 and R_2 are hydrogen, only one of R_1 and R_2 is hydrogen, or neither of R_1 and R_2 are hydrogen, respectively). Where the amine is tertiary, it may be a cyclic amine. Amine substituents R_1 and R_2 may be independently selected from substituents which include hydrogen, alkyl groups containing from one to eight carbon atoms (*i.e.*, C_1-C_8alkyl), alkoxyalkyl groups containing from three to eight carbon atoms (*i.e.*, C_3-C_8alkoxyalkyl), alkyl groups containing from one to eight carbon atoms where one of the carbon atoms is substituted with a hydroxyl group (*i.e.*, C_1-C_8hydroxyalkyl), and aralkyl groups containing from seven to twelve carbon atoms (*i.e.*, C_7-C_{12}aralkyl).

Alternatively, R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a ring denoted by formula (II):

Preferably, R_1 and R_2, when taken together, contain only a single heteroatom. Preferred heteroatoms include nitrogen, oxygen and sulfur. An example of a ring in which R_1 and R_2 together include an oxygen heteroatom is the morpholinyl group. An example of a ring where R_1 and R_2 together include a second nitrogen heteroatom is the piperazinyl group.

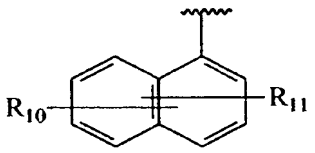
Cyclohexane substituents R_3 and R_4 may be independently attached to ring positions 3, 4, 5 or 6 (*i.e.*, both R_3 and R_4 may be attached to the same ring position or each attached to different ring positions). R_3 and R_4 are independently selected from hydrogen, hydroxy, C_1-C_6alkyl, and C_1-C_6alkoxy, and, when both R_3 and R_4 are attached to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur. Preferred heterocyclic substituents contain either a single oxygen or a single sulfur ring atom.

Depending upon the identity of X, the ether side chain, -CH(R_5)-X-A, in formula (I) may take several forms. For example, a compound of formula (I) may have X as a -C(R_6,R_{14})-Y- group, where Y may be any of a direct bond, an oxygen atom (O), a sulfur atom (S) or a C_1-C_4alkylene group. R_6 and R_{14} are independently selected from hydrogen, C_1-C_6alkyl, aryl and benzyl, or R_6 and R_{14}, when taken together with the carbon to which they are attached, may form a spiro C_3-C_5cycloalkyl. Thus, compounds of the invention include compounds of formula (I) where R_6 and R_{14} are hydrogen and Y is a direct bond, such that X may be CH_2.

Alternatively, X may be an alkenylene moiety, *e.g.*, a *cis*-or *trans*-alkenylene moiety, C(R_{13})=CH, where R_{13} may be any of hydrogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl or benzyl. For compounds of formula (I) where X is an alkenylene moiety, X is preferably a *trans*-alkenylene moiety.

Alternatively, X may be a direct bond. Independent of the selections for A, X and other variables, R_5 is selected from hydrogen, C_1-C_6alkyl, aryl and benzyl.

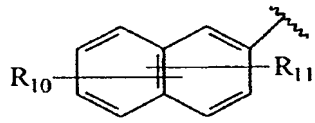
Ether side chain component A is generally a hydrophobic moiety. Typically, a hydrophobic moiety is comprised of non-polar chemical groups such as hydrocarbons or hydrocarbons substituted with halogens or ethers or heterocyclic



(IV)

where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl.

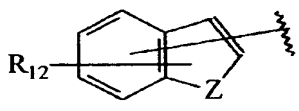
Other suitable "A" groups in compounds of the present invention are 2-naphthyl group as represented by formula (V):



(V)

where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl, as defined above.

Other suitable "A" groups in compounds of the present invention are aromatic groups represented by formula (VI):

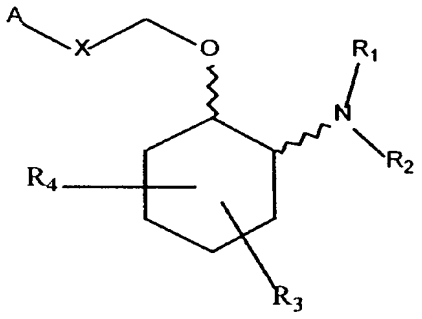


(VI)

Preferably, ether side chain component A is an acenapthyl or fluorenyl group only when X is a direct bond or CH_2. In further preferred embodiments, the acenaphthyl group is a 1-acenaphthyl group, and the fluorenyl group is a 9-fluorenyl group.

As mentioned above, the present invention provides aminocyclohexyl ethers represented by formula (I). In a preferred embodiment X is (CH_2)-Y. For these embodiments, Y is preferably a direct bond, an oxygen atom, or a sulfur atom. In a particularly preferred embodiment, Y is a direct bond or an oxygen atom. In another preferred embodiment Y is a direct bond and X is $C(R_6,R_{14})$, where R_6 and R_{14} are as defined above. In another preferred embodiment, where X is $C(R_{13})$=CH, R_{13} is a hydrogen atom. For these embodiments, R_3 and R_4 are preferably independently attached to the cyclohexane ring at the 4- or 5- positions.

In a preferred embodiment, the invention provides compounds having formula (IX), or a solvate or pharmaceutically acceptable salt thereof:



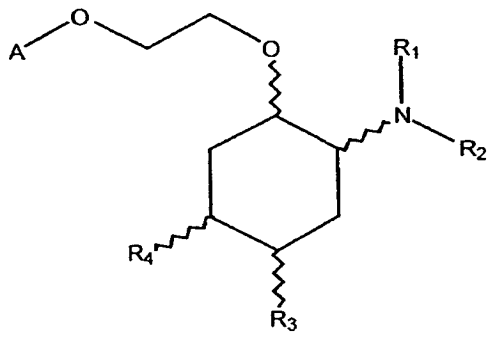
(IX)

wherein, independently at each occurrence,

X is selected from a direct bond, -CH=CH- and $-C(R_6,R_{14})$-Y-;

Y is selected from a direct bond, O and S; and

R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, A and Z are defined as above for compounds of formula (I).



(XI)

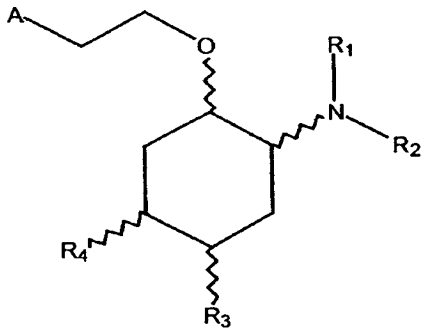
wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5-C_{12}alkyl, C_3-C_8cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as above for compounds of formula (I), wherein Z, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are defined as above for compounds of formula (I).

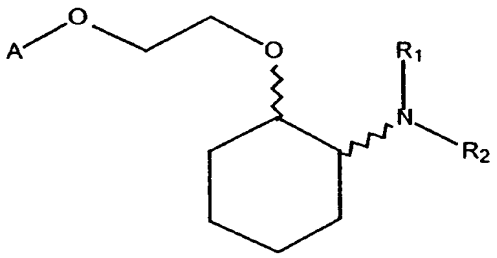
In another preferred embodiment, the invention provides compounds of formula (XII), or a solvate or pharmaceutically acceptable salt thereof:



(XII)

wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);;



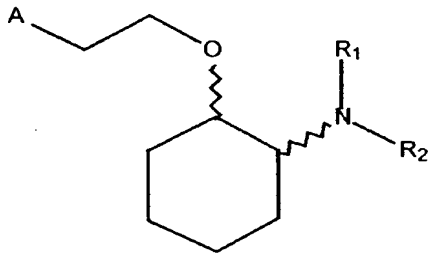
(XIV)

wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);

A is selected from any of formulae (III), (IV), (V) and (VI) as above for compounds of formula (I), wherein R_7, R_{10}, R_{11}, and R_{12}, are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2, with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S.

In another preferred embodiment, the invention provides compounds having formula (XV), or a solvate or pharmaceutically acceptable salt thereof:



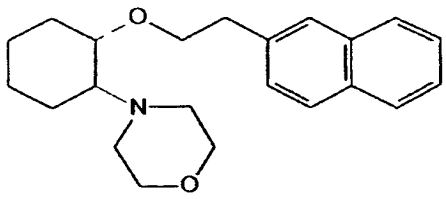
(XV)

wherein, independently at each occurrence,

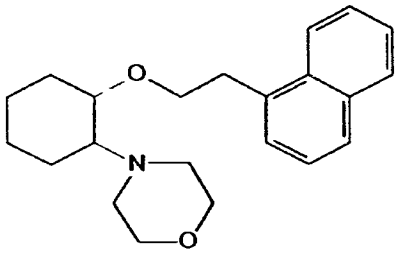
R_1 and R_2 are defined as above for compounds of formula (I); and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined above for compounds of formula (I), wherein R_7, R_{10}, R_{11}, and R_{12}, are hydrogen, R_8 and

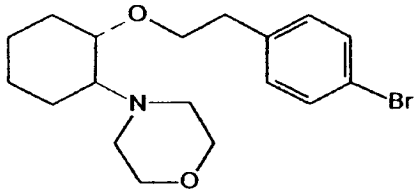
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane



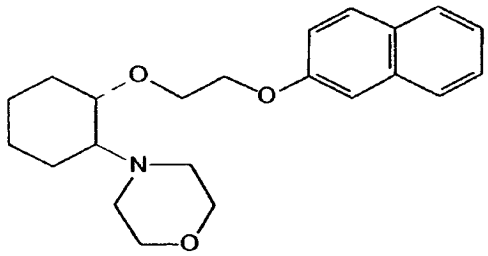
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane



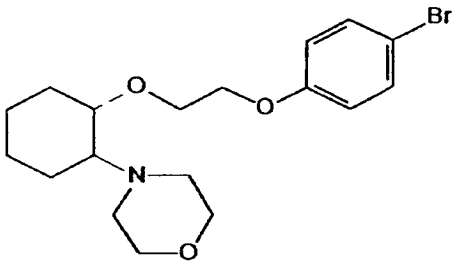
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane



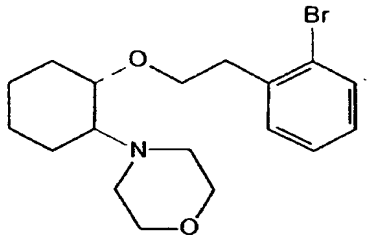
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy]]cyclohexane



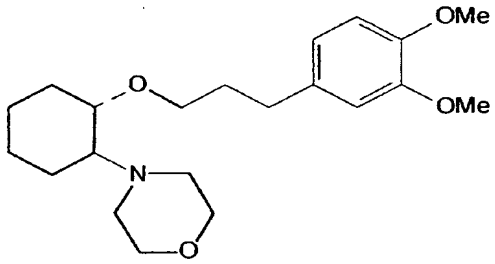
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane



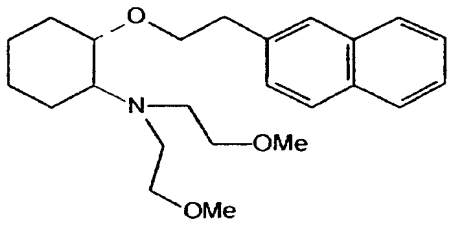
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane



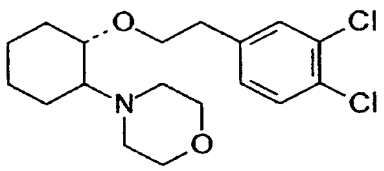
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)propoxy)]cyclohexane



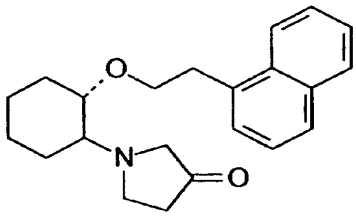
(1R,2R)/(1S,2S)-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane



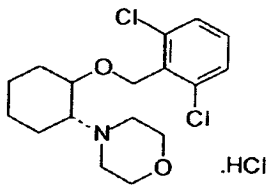
(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-(3,4-dichlorophenethoxy)cyclohexane



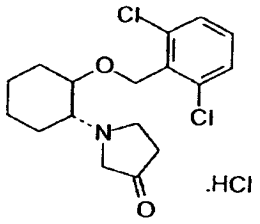
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane



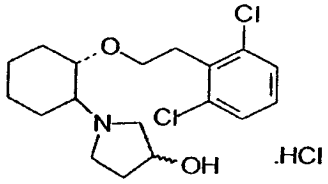
(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane monohydrochloride



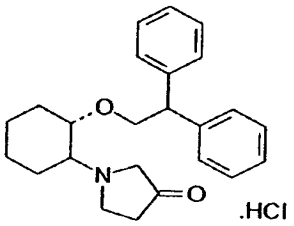
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane monohydrochloride



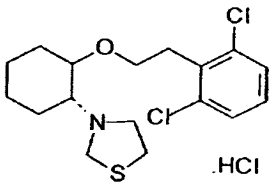
(1R,2R)/(1S,2S)-2-(3-hydroxypyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane monohydrochloride



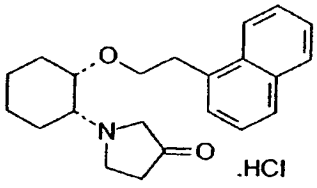
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane monohydrochloride



(1R,2R)/(1S,2S)-2-(3-thiazolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane monohydrochloride



(1R,2S)/(1S,2R)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride



Outline of Method of Preparation of Compounds of the Invention

The aminocyclohexyl ether compounds of the present invention contain amino and ether sidechains disposed in a 1,2 arrangement on a cyclohexane ring.

group. However, the hydroxy group could be converted into other leaving groups according to procedures well known in the art. In a typical reaction, the aminocyclohexanol compound is treated with methanesulfonyl chloride in the presence of a base, such as triethylamine as shown in Figure 1. The reaction is satisfactorily conducted at about 0°C. An excess of the methanesulfonyl chloride, relative to the aminocyclohexanol, is typically preferred in order to maximally convert the more valuable aminocyclohexanol into the activated form. For some other aminocyclohexanol compounds, it may be necessary to introduce appropriate protection groups prior to step ii) being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

In a third step (denoted "iii)" in Figure 1) an alcohol is reacted with a strong base to provide an alkoxide salt. Conversion of an alcohol to an alkoxide (also known as an alcoholate) using strong base is a general reaction, and will work with a wide variety of hydroxy-containing compounds. In some instances, the alcohol compound may have other reactive functional groups that are desirably protected prior to contact of the alcohol with strong base. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). Such alcohols are either commercially available or may be obtained by procedures described in the art or adapted therefrom, where suitable procedures may be identified through the Chemical Abstracts and Indices therefor, as developed and published by the American Chemical Society.

In a fourth step (denoted "iv)" in Figure 1), the alcoholate of step "iii)" is reacted with the activated aminocyclohexanol of step "ii)". Thus, generally stated, compounds of the present invention may be prepared by reacting an activated form of the appropriate 1,2-aminocyclohexanol (1 mol) with an alcoholate (1.25 mol) prepared by treatment of the selected alcohol (1.25 mol) with, for example, sodium hydride (1.3 mol). The 1,2-aminocyclohexanol (1 mol) can be activated by forming the corresponding mesylate, in the presence of methanesulfonyl chloride (1.25 mol) and triethylamine (1.5 mol). The mesylate is added quickly to the alcoholate, in a suitable

953, 1962). The racemic *cis*-ether can be resolved by preparative chiral HPLC as discussed above for the *trans*-compound.

Alternatively, *cis* and *trans* compounds of the invention may be prepared according to the chemistry outlined in Figure 3. As shown in Figure 3, cyclohexene oxide can react with an alcohol (ROH) in the present of $Mg(ClO_4)_2$ (*see, e.g.*, M. Chini et al., *Synlett*, 673-676, 1992) to provide 1,2-hydroxycyclohexyl ethers. Oxidation with pyridinium dichromate (*see, e.g.*, R. Oshima et al., *J. Org. Chem.*, 50, 2613-2621, 1985) yielded the corresponding 1,2-alkoxycyclohexanone. Subsequent reductive amination (R. F. Borch et al., *J. Am. Chem. Soc.*, 93(12), 2897-2904, 1971) provides a mixture of *cis*- and *trans*-aminocyclohexyl ethers. The mixture of diastereomeric ethers can be separated by chromatography by one of ordinary skill in the art. The racemic *cis*- or *trans*-ether so prepared could then be resolved by classical recrystallization methods well known in the art or by preparative chiral HPLC to provide the individual enantiomer: *trans*-(1R,2R), *trans*-(1S,2S), *cis*-(1R,2S) or *cis*-(1S,2R) aminoethers.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to those of ordinary skill in the art to perform the synthesis, isolation, and purification of the compounds of the present invention.

Compositions and Modes of Administration

In another embodiment, the present invention provides compositions which include a cyclohexylamine compound as described above in admixture or otherwise in association with one or more inert carriers, excipients and diluents, as well as optional ingredients if desired. These compositions are useful as, for example, assay standards, convenient means of making bulk shipments, or pharmaceutical compositions. An assayable amount of a compound of the invention is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of the invention will generally vary from about 0.001 wt% to about 75 wt% of the entire weight of the composition. Inert carriers include any material which does not degrade

anesthesia. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of subject (*e.g.*, human), the particular form of the active ingredient, the manner of administration and the composition employed.

In general, the pharmaceutical composition includes a cyclohexylamine compound as described herein, in admixture with one or more carriers. The carrier(s) may be particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier(s) may be gaseous, so as to provide an aerosol composition useful in, *e.g.*, inhalatory administration.

When intended for oral administration, the composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition may be formulated into a powder, granule, compressed tablet, pill, capsule, cachet, chewing gum, wafer, lozenges, or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following adjuvants may be present: binders such as syrups, acacia, sorbitol, polyvinylpyrrolidone, carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin, and mixtures thereof; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; fillers such as lactose, mannitols, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof; lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid, silica, wetting agents such as sodium lauryl sulfate, glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, and a coloring agent.

invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral compositions contain between about 4% and about 50% of the active cyclohexylamine compound. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of active compound.

The pharmaceutical composition may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment, cream or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the inventive compound of from about 0.1 to about 25% w/v (weight per unit volume).

The composition may be intended for rectal administration, in the form, *e.g.*, of a suppository which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol. Low-melting waxes are preferred for the preparation of a suppository, where mixtures of fatty acid glycerides and/or cocoa butter are suitable waxes. The waxes may be melted, and the cyclohexylamine compound is dispersed homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The composition may include various materials which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials which form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule or cachet.

The pharmaceutical compositions may be prepared by methodology well known in the pharmaceutical art. The aminocyclohexyl compounds of the invention may be in the form of a solvate in a pharmaceutically acceptable solvent such as water or physiological saline. Alternatively, the compounds may be in the form of the free base or in the form of a pharmaceutically acceptable salt such as the hydrochloride, sulfate, phosphate, citrate, fumarate, methanesulfonate, acetate, tartrate, maleate, lactate, mandelate, salicylate, succinate and other salts known in the art. The appropriate salt would be chosen to enhance bioavailability or stability of the compound for the appropriate mode of employment (*e.g.*, oral or parenteral routes of administration).

A composition intended to be administered by injection can be prepared by combining the cyclohexylamine compound with water, and preferably buffering agents, so as to form a solution. The water is preferably sterile pyrogen-free water. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the cyclohexylamine compound so as to facilitate dissolution or homogeneous suspension of the cyclohexylamine compound in the aqueous delivery system. Surfactants are desirably present in aqueous compositions of the invention because the cyclohexylamine compounds of the present invention are typically hydrophobic. Other carriers for injection include, without limitation, sterile peroxide-free ethyl oleate, dehydrated alcohols, propylene glycol, as well as mixtures thereof.

Suitable pharmaceutical adjuvants for the injecting solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediaminetetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, epidurally, intraperitoneally, or intravenously.

bone marrow transplantation, heart failure, hypotension, Alzheimer's disease or other mental disorder, and alopecia.

Furthermore, the present invention provides a method for producing local analgesia or anesthesia in a warm-blooded animal which includes administering to a warm-blooded animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutical composition containing a compound of formula (I). These methods may be used to relieve or forestall the sensation of pain in a warm-blooded animal.

Furthermore, the present invention provides a method wherein a preparation that contains ion channels is contacted with, or a warm-blooded animal (*e.g.*, a mammal, such as a human) is administered an effective amount of an aminocyclohexyl ether compound of the invention. Suitable preparations containing cardiac sodium channels include cells isolated from cardiac tissue as well as cultured cell lines. The step of contacting includes, for example, incubation of ion channels with a compound under conditions and for a time sufficient to permit modulation of the activity of the channels by the compound.

In another embodiment, the compounds described above are provided for treating arrhythmia. As used herein, "treating arrhythmia" refers to both therapy for arrhythmia and for the prevention of arrhythmias occurring in a heart that is susceptible to arrhythmia. An effective amount of a composition of the present invention is used to treat arrhythmia in a warm-blooded animal, such as a human. Methods of administering effective amounts of antiarrhythmic agents are well known in the art and include the administration of an oral or parenteral dosage form. Such dosage forms include, but are not limited to, parenteral dosage form. Such dosage forms include, but are not limited to, parenteral solutions, tablets, capsules, sustained release implants, and transdermal delivery systems. Generally, oral or intravenous administration is preferred. The dosage amount and frequency are selected to create an effective level of the agent without harmful effects. It will generally range from a dosage of from about 0.1 to about 100 mg/kg/day, and typically from about 0.1 to 10 mg/kg where administered orally or intravenously for antiarrhythmic effect.

heart rate and the ECG are recorded. In this test, sodium channel blockers produce the ECG changes expected from the first test. In addition, sodium channel blockers also raise the thresholds for induction of extrasystoles and ventricular fibrillation. Potassium channel blockade is revealed by increasing refractoriness and widening of the Q-T intervals of the ECG.

A third test involves exposing isolated rat hearts to increasing concentrations of a compound. Ventricular pressures, heart rate, conduction velocity and ECG are recorded in the isolated heart in the presence of varying concentrations of the compound. The test provides evidence for direct toxic effects on the myocardium. Additionally, selectivity, potency and efficacy of action of a compound can be ascertained under conditions simulating ischemia. Concentrations found to be effective in this test are expected to be efficacious in the electrophysiological studies.

A fourth test is estimation of the antiarrhythmic activity of a compound against the arrhythmias induced by coronary artery occlusion in anaesthetized rats. It is expected that a good antiarrhythmic compound will have antiarrhythmic activity at doses which have minimal effects on either the ECG, blood pressure or heart rate under normal conditions.

All of the foregoing tests are performed using rat tissue. In order to ensure that a compound is not having effects which are only specific to rat tissue, further experiments are performed in dogs and primates. In order to assess possible sodium channel and potassium channel blocking action *in vivo* in dogs, a compound is tested for effects on the ECG, ventricular epicardial conduction velocity and responses to electrical stimulation. An anesthetized dog is subjected to an open chest procedure to expose the left ventricular epicardium. After the pericardium is removed from the heart a recording/stimulation electrode is sewn onto the epicardial surface of the left ventricle. Using this array, and suitable stimulation protocols, conduction velocity across the epicardium as well as responsiveness to electrical stimulation can be assessed. This information coupled with measurements of the ECG allows one to assess whether sodium and/or potassium channel blockade occurs. As in the first test in rats, a

Other Compositions

The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the above formulae. The kit also includes instructions for the use of the pharmaceutical composition for modulating the activity of ion channels, for the treatment of arrhythmia or for the production of local analgesia and/or anesthesia, and for the other utilities disclosed herein. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for the preparation of an intravenous injection. It will be evident to those of ordinary skill in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

The following examples are offered by way of illustration and not by way of limitation. In the Examples, and unless otherwise specified, starting materials were obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and were of standard grade and purity. "Ether" and "ethyl ether" each refers to diethyl ether; "h." refers to hours; "min." refers to minutes; "GC" refers to gas chromatography; "v/v" refers to volume per volume; and ratios are weight ratios unless otherwise indicated.

mixture was heated to 80°C and then the temperature reduced to 40°C. The resulting yellow solution was poured into ice-water (1500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (500 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 13.4 g of an amber oil which was dissolved in water (150 mL) and the pH of the solution was adjusted to pH 2 with aqueous 1M HCl. The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 7.16 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-chloroform (1:1, v/v) as eluent to yield 4.37 g of the pure free base. The product was dissolved in ethyl ether (80 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (80 mL). An oil came out of the solution, the solvent was evaporated *in vacuo* and the residue dissolved in the minimum amount of warm ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 3.83 g (31% yield) of the title compound, m.p. 158-160°C, having the elemental analysis indicated in Table 1.

EXAMPLE 2

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(1-NAPHTHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #2)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (6.0 g, 32 mmol) and triethylamine (6.8 mL, 48 mmol) in dichloromethane (100 mL) was added via cannula a solution of methanesulfonyl chloride (3.10 mL, 40 mmol) in dichloromethane (50 mL). The addition was completed

crystallization. The crystals were collected to afford 2.30 g of the title compound, m.p. 198-200°C, having the elemental analysis indicated in Table 1.

EXAMPLE 3

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(4-BROMOPHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #3)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (25 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (25 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (25 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.7 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.62 g, 25.8 mmol) in dry dimethylformamide (25 mL) was added via cannula a solution of 4-bromophenethylalcohol (4.0 g, 20 mmol) in dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 4 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the slurry of alcoholate. The reaction mixture was heated to 80°C for 2 hours, then the temperature was reduced to 35°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (150 mL) and

mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.3 g (100% yield) of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.7 g, 29 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-(2-naphthoxy)ethanol (3.76 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The resulting reaction mixture was heated overnight to 90°C and then cooled to room temperature. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.8 g of a yellow oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). The resulting precipitate was collected, partially solubilized in water (200 mL) and the heterogeneous aqueous solution was extracted with ether (2 x 100 mL). The remaining insoluble material was collected and recrystallized in boiling ethanol (75 mL) to provide a first crop of the desired product. The acidic aqueous solution was basified to pH 10 with aqueous 50% NaOH and extracted with ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to provide 1.6 g of the crude free amino ether. The product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl acetate-dichloromethane as eluent to yield 0.73 g of a pale yellow oil. The pure free base was then dissolved in ether (50 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ether (50 mL). The white precipitate was collected and recrystallized in boiling ethanol (40 mL) to provide a second crop. Combination of the two crops afforded 1.03 g of the title compound, m.p. 235-237°C, having the elemental analysis indicated in Table 1.

boiling ethanol (150 mL) to yield 3.7 g (54% yield) of the pure title compound, m.p. 228-230°C, having the elemental analysis indicated in Table 1.

EXAMPLE 6

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(3,4-DIMETHOXYPHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #6)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.18 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.64 g, 27 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 3,4-dimethoxyphenethyl alcohol (3.64 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 80°C for 90 min. and then the temperature was reduced to 40°C and stirring continued overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.18 g of the

mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 3.24 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 ml), (0.64 g, 27 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 1-naphthenethanol (3.64 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 80°C for 90 min. and then its temperature was reduced to 40°C and it was stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution with sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 9.00 g of the crude product which was dissolved in ether (50 mL) and treated with a saturated solution of HCl in ether (50 mL). The solvent was evaporated *in vacuo* and the residual oil was taken up with water (100 mL) and extracted with ether (2x50 mL). The aqueous layer was basified to pH10 with 50% NaOH aqueous solution and extracted with ether (2x50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl methanol and chloroform (2:8, v/v) as eluent. The free amino ether was partially dissolved in ether (80 mL), insoluble materials were filtered off, and then a saturated solution of HCl in ether (80 mL) was added to the filtrate. The solvent was evaporated *in vacuo*, the residue was dissolved in acetone and addition of aliquots of ether triggered slow crystallization. 2 crops of the title compound (0.88 g), m.p. 103-105°C were collected, having the elemental analysis indicated in Table 1.

and the resulting crude hydrochloride salt was dissolved in water (200 ml). The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with aqueous 50% sodium hydroxide. The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.30 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate and dichloromethane (1:1, v/v) as eluent to provide the free base. The product was dissolved in ethyl ether (100 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (100 mL). The solvent was evaporated *in vacuo* and the residue was dissolved in the minimum amount of boiling methanol to provide a first crop (0.7 g) of crystalline product on cooling. Addition of diethyl ether to the methanol filtrate provided a second crop (0.55 g). The two crops were combined to yield 1.25 g of the title compound, m.p. 158-160°C, having the elemental analysis indicated in Table 1.

EXAMPLE 9

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(2-(BENZO[B]THIOPHEN-4-YL)ETHOXY)] CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #9)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24.0 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20,0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.24 g of the crude mesylate.

EXAMPLE 10

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(3-BROMOPHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #10)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 5.4 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 3-bromophenethyl alcohol (4.0 g, 20 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 85°C for 2 hours, then the temperature was reduced to 45°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.0 g of an oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). An oil precipitated and the solvent was evaporated *in vacuo* and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution

via cannula a solution of 2-bromophenethyl alcohol (4.0 g, 20 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 85°C for 2 hours, then the temperature was reduced to 45°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.4 g of an oil which was dissolved in 1.0 M HCl aqueous solution (50 mL), the volume was adjusted to 200 mL with water and the pH adjusted to pH 2 with 1.0 M HCl aqueous solution. The acidic aqueous solution was extracted with ethyl ether (3 x 100 mL) and then basified to pH 10 with 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 2.8 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (50 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (50 mL). The solvent was evaporated *in vacuo*, the residue was dissolved in the minimum amount of cold ethanol and addition of ether triggered formation of crystals which were collected in two crops (0.74 g), m.p. 140-142°C, having the elemental analysis indicated in Table 1.

NaOH aqueous solution and extracted with ether (2x100 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl acetate and dichloromethane (1:1, v/v) as eluent to provide the free base which was dissolved in ether (80 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ether (80 mL). The sticky precipitate was collected, dissolved in the minimum amount of warm ethanol and a large excess of ether was added to trigger crystallization of the title compound, m.p. 175-177°C, having the elemental analysis indicated in Table 1.

EXAMPLE 13

(±)-TRANS-[2-[BIS(2 METHOXYETHYL)AMINO]-1-(2-NAPHTHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #13)

(i) Bis-(2-methoxyethyl)amine(25 mL, 169 mmol) and cyclohexene oxide (17.2 mL, 170 mmol) were mixed in water (5 mL) and the resulting mixture was refluxed for 30 hours. The cooled reaction mixture was partitioned between 10% NaOH aqueous (200 mL) and diethyl ether (200 mL). The aqueous layer was extracted twice more with diethyl ether (2 x 100 mL), the combined organic layers were washed with water (8 mL) and dried over sodium sulfate. The solvent was evaporated *in vacuo* to provide the crude product which was vacuum distilled to provide 26.4 g of pure colorless oil.

(ii) To a chilled (0°C) solution of (±)-*trans*-2-[bis(2-methoxyethyl)amino]cyclohexanol) 4.63 g, 20.00 mmol) and triethylamine (3.4 mL, 24.00 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.00 mmol) in dichloromethane (50 mL). The additional was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings backextracted with

EXAMPLE 14

(1R,2R)/(1S,2S)-2-(4-MORPHOLINYL)-1-(3,4-DICHLOROPHENETHOXY) CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #14)

The basic overall approach used to synthesize this compound is analogous to that shown in Figure 1.

(i) (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclohexanol: A mixture of cyclohexene oxide (206.5 mL, 2 mol, 98%) and morpholine (175 mL, 2 mol) in water (60 mL) was refluxed for 3.5 h. Morpholine (5.3 mL) was added to the reaction mixture, which was then further refluxed for 1.5 h. in order to complete the reaction. The cooled reaction mixture was then partitioned between 40% NaOH aqueous solution (100 mL) and diethyl ether (200 mL). The aqueous layer was separated from the organic layer and extracted twice more with diethyl ether (2 x 100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Vacuum distillation yielded 342.3 g (92.4%) of the title compound.

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexanol (40.76 g, 0.22 mol) and triethylamine (36.60 mL, 0.26 mol) in dichloromethane (400 mL) was added dropwise a solution of methanesulfonyl chloride (20.53 mL, 0.26 mol) in dichloromethane (50 mL). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was then washed with water (2 x 100 mL); the combined washings were back-extracted with dichloromethane (100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate suitable for the next step without any further purification.

(iii) 3,4-Dichlorophenethyl alcohol: To a solution of lithium aluminum hydride (7.79 g, 195 mmol) in anhydrous diethyl ether (435 mL) was added slowly as a powder, via a solid dropping funnel, 3,4-dichlorophenyl acetic acid (27.20 g, 130 mmol). When the addition was completed, the reaction mixture was refluxed for 12 hours. The reaction was quenched by cautious addition of saturated sodium sulfate

EXAMPLE 15

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-(1-NAPHTHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #15)

Synthesis of Compound #15 follows the sequence of reactions shown in Figure 4A and Figure 4B, and is described in detail below.

(i) N-Benzyloxycarbonyl-3-pyrrolidinol: To a chilled (-60°C) solution of (R)-(+)-3-pyrrolidinol (20.0 g, 98%, 224.9 mmol) and triethylamine (79.2 mL, 99%, 562 mmol) in dichloromethane (200 mL) was added dropwise a solution of benzyl chloroformate (33.8 mL, 95%, 224.9 mmol) in dichloromethane (80 mL). After the addition was completed within 45 min, the reaction mixture (a yellow suspension) was allowed to warm up to room temperature and was stirred under argon at room temperature overnight. The reaction mixture was then quenched with 1M HCl aqueous solution (350 mL) and the organic layer was collected. The acidic aqueous layer was extracted with dichloromethane (2 x 150 mL) and the combined organic layers were dried over sodium sulfate. Evaporation *in vacuo* of the solvent provided 59.62 g of pale yellow oil, which was further pumped under high vacuum for 15 min to yield 58.23 g (17% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

(ii) N-Benzyloxycarbonyl-3-pyrrolidinone: To a chilled (-60°C) solution of oxalyl chloride (23 mL, 98%, 258.6 mmol) in dichloromethane (400 mL) was added dropwise a solution of anhydrous dimethyl sulfoxide (36.7 mL, 517.3 mmol) in dichloromethane (20 mL) at such a rate to keep the temperature below -40°C. The reaction mixture was then stirred at -60°C for 15 min. Then a solution of N-benzyloxycarbonyl-3-pyrrolidinol (58.22 g, step i, no more than 224.9 mmol) in dichloromethane (80 mL) was added dropwise, keeping the reaction mixture temperature below -50°C. The reaction mixture was then stirred at -60°C for 30 min before adding triethylamine (158.3 mL, 99%, 1.125 mol). The resulting mixture was allowed to warm up to room temperature and then washed with water (600 mL), 1M

40% sodium hydroxide aqueous solution (60 mL) and diethyl ether (120 mL). The basic aqueous layer was extracted twice more with diethyl ether (2 x 120 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue was then pumped under high vacuum at 50 °C for 1 hour under stirring (to remove the excess of cyclohexene oxide) to yield 32.79 g of the crude title compound (yield 79.3%).

(vi) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol (27.47 g, 120 mmol, step v) and triethylamine (15.86 g, 156 mmol) in dichloromethane (240 mL) was added dropwise methanesulfonyl chloride (18.23 g, 156 mmol). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was then washed with a mixture of water-saturated sodium bicarbonate aqueous solution (1:1, v/v, 120 mL). The washing layer was collected and was back-extracted with dichloromethane (120 mL). The combined organic extracts were dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was pumped under high vacuum for 4 hours to yield the crude mesylate suitable for the next step without any further purification.

(vii) To sodium hydride (4.32 g, 144 mmol) suspended in anhydrous ethylene glycol dimethyl ether (80 mL) was added a solution of 1-naphthenethanol (25.31 g, 144 mmol) in anhydrous ethylene glycol dimethyl ether (80 mL). The resulting mixture was then stirred at room temperature for 4 hours.

(viii) (1R,2R)/(1S,2S)-2-[1,4-dioxa-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane: A solution of mesylate (vi) in anhydrous ethylene glycol dimethyl ether (80 mL) was added quickly to the alkoxide (vii) and the resulting mixture was readily heated to reflux under argon for 66 hours. The cooled reaction mixture was quenched with water (200 mL) and the organic solvent was evaporated *in vacuo*. The remaining aqueous solution was diluted with water (500 mL) and acidified with 10% HCl aqueous solution to pH 0.5. The acidic aqueous layer was extracted with diethyl ether (2 x 500 mL) in order to extract unreacted 1-naphthenethanol. The pH of the aqueous solution was adjusted to pH 4.8 with 5M NaOH aqueous solution and then

EXAMPLE 16

(1R,2R)/(1S,2S)-2-(1-ACETYLPIPERAZINYL)-1-(2-NAPHTHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #16)

Compound #16 was prepared according to a procedure similar as the one depicted in Figure 1 and further detailed in Example 14.

(i) (1R,2R)/(1S,2S)-2-(1-Acetylpiperazinyl)-1-cyclohexanol: A mixture of 1-acetylpiperazine (5 g, 39 mmol) and cyclohexene oxide (3.95 mL, 39 mmol) in water (1.2 mL) was refluxed for 16 hours. The cooled reaction mixture was partitioned between 40% NaOH aqueous solution (20 mL) and diethyl ether (2 x 20 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 7.63 g of the title compound as white crystals (87% yield)

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1-acetylpiperazinyl)-1-cyclohexanol (3.65 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added dropwise a solution of methanesulfonyl chloride (1.55 mL, 20 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at 0°C for one hour and then allowed to warm up to ambient temperature. The reaction mixture was then washed with water (2 x 50 mL) and the combined washings were back-extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate suitable for the next step without any further purification.

(iii) To a suspension of sodium hydride (0.8 g, 24 mmol, previously washed with hexanes (2 x 15 mL)) in anhydrous dimethylformamide (50 mL) was added a solution of 2-naphthenethanol in anhydrous dimethylformamide (50 mL). The resulting mixture was stirred at room temperature for 30 min.

(iv) (1R,2R)/(1S,2S)-2-(1-Acetylpiperazinyl)-1-(2-naphthenethoxy)cyclohexane monohydrochloride: the mesylate (ii) in solution in anhydrous dimethylformamide (50 mL) was added quickly to the alkoxide mixture (iii) and the resulting mixture was heated to 80°C for 16 hours. The cooled reaction mixture

evaporated *in vacuo* to yield the crude mesylate which was further pumped under high vacuum for 4 hours prior to use in step ix.

(vii) 2,6-Dichlorophenethyl alcohol: a suspension of lithium aluminum hydride (13.75 g, 365.75 mmol) in anhydrous diethyl ether (500 mL) was added via a powder addition funnel 2,6-dichlorophenylacetic acid (50 g, 243.75 mmol). The resulting reaction mixture was refluxed for 16 hours and then quenched by slow addition of a sodium sulfate saturated aqueous solution (25 mL). The resulting slurry was stirred for 3 hours and then filtered, the insoluble was carefully washed with diethyl ether (2 x 100 mL). The combined ether filtrates were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 38.6 g (85% yield) of the title compound.

(viii) To sodium hydride (144 mmol, 4.32 g, 80% oil dispersion) in anhydrous ethylene glycol dimethyl ether (80 mL) was added a solution of 2,6-dichlorophenethyl alcohol (27.65 g, 144 mmol) in anhydrous ethylene glycol dimethyl ether (80 mL). The resulting mixture was stirred at room temperature under argon atmosphere for 4 hours.

(ix) (1R,2R)/(1S,2S)-2-[1,4-Dioxa-7-azaspiro[4.4]non-7-yl]-1-(2,6-dichlorophenethoxy)cyclohexane: The mesylate (vi) in anhydrous ethylene glycol dimethyl ether (80 mL) was added quickly to the alkoxide mixture (viii) and the resulting mixture was readily refluxed for 66 hours. The cooled reaction mixture was poured into water (200 mL) and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was diluted with more water to a volume of 700 mL, acidified to pH 0.5 with 6M HCl aqueous solution and extracted with diethyl ether (2 x 600 mL). The pH of the aqueous layer was adjusted to pH 5.9 and then the aqueous solution was extracted with diethyl ether (700 mL). The organic extract was dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 34.0 g of the title compound (70% yield).

(x) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane monohydrochloride: A mixture of (1R,2R)/(1S,2S)-2-[1,4-dioxa-7-azaspiro[4.4]non-7-yl]-1-(2,6-dichlorophenethoxy)cyclohexane (15.85 g, 38.9 mmol, step ix) and 6M HCl aqueous solution (100 mL) in 2-butanone (400 mL)

EXAMPLE 19

(1R,2S)/(1S,2R)-2-(4-MORPHOLINYL)-1-[(2-TRIFLUOROMETHYL)PHENETHOXY]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #19)

(i) 2-(4-Morpholinyl)cyclohexanone: To a chilled (-70°C) solution of oxalyl chloride (20 mL, 0.23 mol) in dichloromethane (500 mL) was added dropwise a solution of anhydrous dimethylsulfoxide (34 mL, 0.48 mol) in dichloromethane (50 mL) and the resulting mixture was stirred for 5 min. at a temperature below -60°C. Then a solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexanol (37.05 g, 0.2 mol) in dichloromethane (50 mL) was added dropwise in order to maintain the reaction temperature below -60°C and the reaction mixture was stirred for 15 min. Triethylamine (140 mL) was added dropwise to the reaction mixture, keeping the reaction temperature below -50°C, and then the reaction mixture was allowed to warm up to room temperature. The reaction mixture was poured into water (600 mL) and the aqueous layer was separated and extracted with dichloromethane (2 x 500 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Vacuum distillation yielded 35.1 g (96% yield) of the title compound.

(ii) 2-(4-Morpholinyl)cyclohexanol: To a chilled (0°C) suspension of sodium borohydride (2.14 g, 56 mmol) in isopropanol (120 mL) was added a solution of 2-(4-morpholinyl)cyclohexanol (24.7 g, 135 mmol, step i) in isopropanol (80 mL). The resulting reaction mixture was stirred at 0°C for 10 min. and then 30 min. at ambient temperature. Water (200 mL) was added to the reaction mixture and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was then extracted with ethyl acetate (4 x 50 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 22.48 g of the title compound suitable for the next step without any further purification.

(iii) (1S,2R)/(1R,2S)-2-(4-Morpholinyl)cyclohexyl 2-(trifluoromethyl)phenylacetate: A mixture of 2-(4-morpholinyl)cyclohexanol (7.41 g, 40 mmol, step ii), 2-(trifluoromethyl)phenylacetic acid (10.21 g, 49 mmol) and p-

dichloromethane (10 mL). The acidic aqueous solution was extracted once more with dichloromethane (10 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Recrystallization from a mixture of ethanol-hexanes yielded 636 mg (38% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 20

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-[3-(CYCLOHEXYL)PROPOXY]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #20)

(i) 3-Cyclohexyl-1-propyl bromide: To the chilled (0°C) 3-cyclohexyl-1-propanol (5 g, 35.15 mmol) was added slowly a solution of phosphorus tribromide (1.1 mL, 17.6 mmol) in dichloromethane (2 mL). Upon completion of the addition, the reaction mixture was allowed to warm up to room temperature and was stirred for 4 hours. The reaction was quenched by addition of saturated sodium bicarbonate aqueous solution (5 mL) and 10% NaOH (10 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to provide an oil. Vacuum distillation yielded 3.4 g (47% yield) of the title compound.

(ii) (1R,2R)/(1S,2S)-2-[1,4-Dioxa-7-azaspiro[4.4]non-7-yl]-1-[3-(cyclohexyl)propoxy]cyclohexane: To a suspension of sodium hydride (200 mg, 8.33 mmol) in anhydrous dimethylformamide (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol (1.5 g, 6.6 mmol) in anhydrous dimethylformamide (10 mL). The resulting mixture was stirred at room temperature for 30 min. and then a solution of 3-(cyclohexyl)propyl bromide (1.67 g, 8.15 mmols) in anhydrous dimethylformamide was quickly added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (200 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were back-washed with brine (50 mL) and the solvent was evaporated

the reaction mixture was evaporated to dryness and the residue was washed with dichloromethane (2 x 20 mL). The dichloromethane washings were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the title compound.

(ii) (1R,2R)/(1S,2S)-2-(3-Acetoxypyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride: The intermediate alcohol (i) was then refluxed in acetic anhydride (15 mL) for 2 hours. The excess acetic anhydride was removed *in vacuo*; the residue was taken up with water (100 mL) and extracted with diethyl ether (2 x 30 mL). The aqueous solution was basified to pH 8.0 and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The residual oil was dissolved in a small amount of dichloromethane and a large volume of diethyl ether was added in order to trigger crystallization of 1.0 g (65% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 22

(1R,2R)/(1S,2S)-2-(4-MORPHOLINYL)-1-[(2,6-DICHLOROPHENYL)METHOXY]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #22)

Compound #22 was prepared according to the Williamson ether synthesis. To a suspension of sodium hydride, 80% oil dispersion (337 mg, 11 mmol) in ethylene glycol dimethyl ether (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-cyclohexanol (2.0 g, 10.8 mmol) in ethylene glycol dimethyl ether (10 mL). The resulting reaction mixture was stirred at room temperature under argon atmosphere for 3 hours, then a solution of 2,6-dichlorobenzyl bromide in ethylene glycol dimethyl ether (10 mL) was added and the reaction mixture was refluxed for 16 hours. The cooled reaction mixture was poured into water (40 mL) and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was diluted with more water (60 mL) and acidified to pH 0.5 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (2 x 40 mL) and then the pH was

(vii) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane monohydrochloride: The ketal intermediate (step vi) in a mixture of 6M HCl-butanone (1:4, v/v, 100 mL) was refluxed for 16 hours. The butanone was evaporated *in vacuo* and the residual aqueous layer was diluted with more water (100 mL). The acidic aqueous layer was extracted with diethyl ether (2 x40 mL) and then with dichloromethane (3 x 40 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to provide the crude title compound. The product was crystallized by triturating in diethyl ether and reprecipitated from a mixture of dichloromethane-diethyl ether to yield 1.8 g (72% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 24

(1R,2R)/(1S,2S)-2-(3-HYDROXYPYRROLIDINYL)-1-(2,6-DICHLOROPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #24)

To a solution of compound #17 (5.0 g, 12.7 mmol) in isopropanol (120 mL) was added sodium borohydride (2.0 g, 52.8 mmol) as a powder and the resulting mixture was stirred at room temperature until completion of the reaction. The reaction was quenched with water (40 mL) and then concentrated to dryness. The residue was washed with dichloromethane (50 mL); the filtrate was dried over sodium sulfate, concentrated *in vacuo* to provide the title compound, which crystallized after 3 hours under high vacuum. Elemental analysis results of the product is shown in Table 1.

5 days. The cooled reaction mixture was concentrated *in vacuo*, the residue was taken up with water (50 mL) and the pH was adjusted to pH 1.0 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (2 x 50 mL), the aqueous layer was collected and basified to pH 6.0. Extraction with diethyl ether (2 x 50 mL) followed by drying over sodium sulfate and evaporation of the solvent *in vacuo* yielded 1.55 g (43% yield) of the title compound.

(x) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane monohydrochloride: A mixture of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)-1-(2,2-diphenylethoxy)cyclohexane (1.55 g, 3.8 mmol) in 6M HCl-butanone (1:4, v/v, 50 mL) was refluxed for 2 hours. The butanone was evaporated *in vacuo* and the residue was taken up with water (50 mL). The aqueous solution was extracted with diethyl ether (2 x 50 mL); the aqueous layer was collected and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane extracts were dried over sodium sulfate and concentrated *in vacuo* to yield the crude title compound. The product was crystallized by triturating in diethyl ether and reprecipitated from a mixture of dichloromethane-diethyl ether to yield 1.21 g (80% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 26

(1R,2R)/(1S,2S)-2-(3-THIAZOLIDINYL)-1-(2,6-DICHLOROPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #26)

(i) (1R,2R)/(1S,2S)-2-(3-Thiazolidinyl)cyclohexanol: To anhydrous magnesium perchlorate (12.93 g, 53.3 mmol) was added a solution of cyclohexene oxide (6.1 mL, 58.6 mmol) in anhydrous acetonitrile (25 mL) and the resulting mixture was stirred at room temperature for 20 min. Then a solution of thiazolidine (5.16 g, 55.0 mmol) in anhydrous acetonitrile was added and the reaction mixture was heated at 35°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (350 mL) and diethyl ether (350 mL). The aqueous layer was

hydrochloride salt by treatment with ethereal HCl and the resulting salt was recrystallized from a mixture of acetone-diethyl ether to yield 0.69 g of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 27

(1R,2S)/(1S,2R)-2-(3-KETOPYRROLIDINYL)-1-(1-NAPHTHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #27)

Compound #27 was prepared in 8 steps according to the synthetic scheme depicted in Figure 3. Steps (i) to (iv) were identical to those described in Example 15.

(v) (1R,2R)/(1S,2S)-1-(1-Naphthenethoxy)-2-cyclohexanol: To anhydrous magnesium perchlorate (270 mg, 1.2 mmol) in anhydrous acetonitrile (1.7 mL) was added cyclohexene oxide (0.12 g, 1.2 mmol). The resulting mixture was stirred for 15 min. at room temperature and then 1-naphthenethanol (2.7 g, 10.15 mmol) was added. The reaction mixture was refluxed and more cyclohexene oxide (2.0 mL, 2.0 g, 20 mmol) was added to the refluxing reaction mixture at a rate of 0.4 mL/hour. Reflux was stopped after 16 hours and the cooled reaction mixture was partitioned between diethyl ether (50 mL) and saturated sodium bicarbonate aqueous solution (30 mL). The aqueous layer was separated and extracted twice more with diethyl ether (2 x 40 mL). The combined organic extracts were back-washed with water (15 mL), brine (15 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded the crude title compound suitable for the next step without any further purification.

(vi) 1-(1-Naphthenethoxy)-2-cyclohexanone: To a solution of (1R,2R)/(1S,2S)-2-(1-naphthenethoxy)-1-cyclohexanol (1.0 g, step v) in dimethylformamide (20 mL) was added pyridinium dichromate (5.0 g, 13.2 mmol) in small portions and the resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (100 mL) and the resulting slurry was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were

was diluted to 50 mL with water and extracted twice with diethyl ether (2 x 50 mL) and then thrice with dichloromethane (3 x 50 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*, the residual oil was further dried by azeotropic distillation of toluene. The title compound was crystallized by triturating in hexanes (430 mg, 93% yield), and has elemental analysis indicated in Table 1.

EXAMPLE 28

ASSESSMENT OF ANTIARRHYTHMIC EFFICACY

Antiarrhythmic efficacy was assessed by investigating the effect of a compound on the incidence of cardiac arrhythmias in conscious rats subject to coronary artery occlusion. Rats weighing 200-300 gms were subjected to preparative surgery and assigned to groups in a random block design. In each case, the animal was anesthetized with halothane during surgical preparation. The left femoral artery was cannulated for measurement of mean arterial blood pressure and withdrawal of blood samples. The left femoral vein was also cannulated for injection of drugs. The thoracic cavity was opened and a polyethylene occluder loosely placed around the left anterior descending coronary artery. The thoracic cavity was then closed. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All cannulae and electrode leads were exteriorized in the mid scapular region. In a random and double-blind manner, about 0.5 to 2 hours post-surgery, an infusion of vehicle, or the compound to be tested was given. After 15 minutes infusion, the occluder was pulled so as to produce coronary artery occlusion. ECG, arrhythmias, blood pressure, heart rate and mortality were monitored for 30 minutes after occlusion. Arrhythmias were recorded as ventricular tachycardia (VT) and ventricular fibrillation (VF) and scored according to Curtis, M.J. and Walker, M.J.A., *Cardiovasc. Res. 22*:656 (1988) (*see* Table 2).

Table 3

Compound	ED50AA
#1	0.8
#2	1.0
#3	2.1
#4	2.0
#5	3.0
#6	4.0
#7	4.0
#8	1.0
#9	1.0
#10	2.0
#11	1.0
#14	1.5
#15	0.43
#17	1.1
#19	1.4
#21	1.4
#22	1.8
#23	2.1
#24	0.6
#25	2.5
#26	6.5

EXAMPLE 29

MEASUREMENT OF ECG PARAMETERS

Rats weighing 200-250 gms were used in this example. Animals were anesthetized with 60 mg/kg pentobarbitone i.p. The carotid artery and jugular vein were cannulated for measurement of blood pressure and drug injection, respectively. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All compounds were given as bolus injections.

Various ECG parameters were measured. Table 4 describes the results of the tests as ED_{25} (micromol/kg) which are the doses required to produce a 25% increase in the parameter measured (ne = not estimated). The increases in P-R interval and QRS interval indicate cardiac sodium channel blockage while the increase in Q-T interval

Table 5

Compound	It	VFT	ERP
#1	2.8	1.4	1.5
#2	0.9	0.7	1.3
#3	5.8	NE	4.0
#7	0.7	0.2	0.4
#14	6.4	-	1.7
#15	5	1.2	1.6
#17	6	7.3	7.1
#23	7.6	6.2	5
#24	1.7	1.2	1.1
#26	10.5	9	5.4

EXAMPLE 31

CANINE VAGAL-AF MODEL

General methods

Mongrel dogs of either sex weighing 15-49 kg were anesthetized with morphine (2 mg/kg im initially, followed by 0.5 mg/kg IV every 2 h) and α-chloralose (120 mg/kg IV followed by an infusion of 29.25 mg/kg/h; St.-Georges et al., 1997). Dogs were ventilated mechanically with room air supplemented with oxygen via an endotracheal tube at 20 to 25 breaths/minute with a tidal volume obtained from a nomogram. Arterial blood gases were measured and kept in the physiological range (SAO_2>90%, pH 7.30-7.45). Catheters were inserted into the femoral artery for blood pressure recording and blood gas measurement, and into both femoral veins for drug administration and venous sampling. Catheters were kept patent with heparinized 0.9% saline solution. Body temperature was maintained at 37-40°C with a heating blanket.

The heart was exposed via a medial thoracotomy and a pericardial cradle was created. Three bipolar stainless steel, Teflon™-coated electrodes were inserted into the right atria for recording and stimulation, and one was inserted into the left atrial appendage for recording. A programmable stimulator (Digital Cardiovascular Instruments, Berkeley, CA) was used to stimulate the right atrium with 2 ms, twice

Measurement of electrophysiological variables and vagal response

Diastolic threshold current was determined at a basic cycle length of 300 ms by increasing the current 0.1 mA incrementally until stable capture was obtained. For subsequent protocols current was set to twice diastolic threshold. Atrial and ventricular ERP was measured with the extrastimulus method, over a range of S1S2 intervals at a basic cycle length of 300 ms. A premature extrastimulus S2 was introduced every 15 basic stimuli. The S1S2 interval was increased in 5 ms increments until capture occurred, with the longest S1S2 interval consistently failing to produce a propagated response defining ERP. Diastolic threshold and ERP were determined in duplicate and averaged to give a single value. These values were generally within 5 ms. The interval between the stimulus artefact and the peak of the local electrogram was measured as an index of conduction velocity. AF cycle length (AFCL) was measured during vagal-AF by counting the number of cycles (number of beats -1) over a 2-second interval at each of the atrial recording sites. The three AFCLs measurements were averaged to obtain an overall mean AFCL for each experimental condition.

The stimulus voltage-heart rate relationship for vagal nerve stimulation was determined under control conditions in most experiments. The vagal nerves were stimulated as described above with various voltages to determine the voltage which caused asystole (defined as a sinus pause greater than 3 seconds). The response to vagal nerve stimulation was confirmed under each experimental condition and the voltage adjusted to maintain the heart rate response to vagal nerve stimulation constant. In cases in which is was not possible to produce asystole, vagal nerve stimulation was adjusted to a voltage which allowed two 20-minute episodes of vagal-AF to be maintained under control conditions (see below).

Experimental protocols

The experimental groups studied are summarized in Table 5. Each dog received only one drug at doses indicated in Table 5. The first series of experiments were dose ranging studies, followed by blinded study in which 1-3 doses were given. All drugs were administered IV via an infusion pump, with drug solutions prepared

Table 6

EXPERIMENTAL GROUPS AND DOSES OF DRUGS

Drug	Dose range tested (μ mol/kg)	Effective doses for terminating AF (μmol/kg)	Mean dose required for termination of AF (μmol/kg)	Median dose required for termination of AF (μmol/kg)
Flecainide	1.25-10	4-2.5; 1-10	4 ± 2	2.5

A single drug was administered to each dog over the dose range specified until AF was terminated. The number of dogs in which AF was terminated at each dose is shown (number of dogs-dose, in μmol/kg). The mean ± SEM as well as the median dose required to terminate AF is shown. Each dog received only one drug.

A number of the compounds of the present invention have been evaluated by this method. The results showed that all of the compounds tested are effective in terminating AF in the canine vagal-AF model. The conversion rates are similar to those reported for a variety of other class I and III drugs in this model. The effectiveness of flecainide as a control in the present study was comparable to that previously reported. All of the drugs prolonged AFCL prior to termination of AF; effects which are globally consistent with the wave length of re-entry model for termination of AF. The tested compounds of the present invention did not reduce blood pressure or heart rate at the median dose for termination of vagal-AF. The heart rate response to vagal nerve stimulation was similar in all groups and was not influenced by any of the compounds tested. Vagal nerve stimulation at 60% of the voltage required to produce asystole (10±1 V) produced a 1.3±0.1 second pause.

EXAMPLE 32

CANINE STERILE PERICARDITIS MODEL

This model has been used to characterize the mechanisms of AF and atrial flutter (AFL). Waldo and colleagues have found that AF depends on reentry and

Creation of the Sterile Pericarditis Atrial Fib/Flutter Model

The canine sterile pericarditis model was created as previously described. At the time of surgery, a pair of stainless steel wire electrodes coated with FEP polymer except for the tip (O Flexon, Davis and Geck) were sutured on the right atrial appendage, Bachman's bundle and the posteroinferior left atrium close to the proximal portion of the coronary sinus. The distance between each electrode of each pair was approximately 5 mm. These wire electrodes were brought out through the chest wall and exteriorized posteriorly in the interscapular region for subsequent use. At the completion of surgery, the dogs were given antibiotics and analgesics and then were allowed to recover. Postoperative care included administration of antibiotics and analgesics.

In all dogs, beginning on postoperative day 2, induction of stable atrial fibrillation/flutter was attempted in the conscious, non-sedated state to confirm the inducibility and the stability of atrial fib/flutter and to test the efficacy of the drugs. Atrial pacing was performed through the electrodes sutured during the initial surgery. On postoperative day 4, when stable atrial flutter was induced, the open-chest study was performed.

For the open-chest study, each dog was anesthetized with pentobarbital (30 mg/kg IV) and mechanically ventilated with 100% oxygen by use of a Boyle model 50 anesthesia machine (Harris-Lake, Inc.). The body temperature of each dog was kept within the normal physiological range throughout the study with a heating pad. With the dog anesthetized, but before the chest was opened, radiofrequency ablation of the His bundle was performed to create complete atrioventricular (AV) block by standard electrode catheter techniques. This was done to minimize the superimposition of atrial and ventricular complexes during subsequent recordings of unipolar atrial electrograms after induction of atrial flutter. After complete AV block was created, an effective ventricular rate was maintained by pacing of the ventricles at a rate of 60 to 80 beats per minute with a Medtronic 5375 Pulse Generator (Medtronic Inc.) to deliver stimuli via the electrodes sutured to the right ventricle during the initial surgery.

6. If AF terminated with the first dose then a blood sample was taken and ERP measurements were repeated.

7. Five minutes was allowed for the drug to terminate. If there was no termination then the second dose was given over 5 minutes.

8. After termination and ERPs were measured, a second attempt to reinduce AF was tried for a period of ten minutes.

9. If reinduced and sustained for 10 minutes, a blood sample was taken and the study repeated from #3 above.

10. If no reinduction, then the study was over.

A number of the compounds of the present invention have been evaluated by this method. The results showed that all of the compounds tested are effective in terminating episodes of atrial fibrillation/flutter in this model. There was no proarrhythmia or cardiovascular adverse events observed during drug treatment.

EXAMPLE 33

IN VITRO ASSESSMENT OF INHIBITION ACTIVITY OF ION CHANNEL MODULATING COMPOUNDS ON DIFFERENT CARDIAC ION CURRENTS

Cell culture:

The relevant cloned cardiac ion channels (*e.g.* Kv1.4, Kv1.5, Kv4.2, Kv2.1 etc.) were studied by transient transfection into HEK cells using the mammalian expression vector pCDNA3. Transfections for each channel type were carried out separately to allow individual study of the ion channel of interest. Cells expressing channel protein were detected by cotransfecting cells with the vector pHook-1 (Invitrogen, San Diego, CA, USA). This plasmid encoded the production of an antibody to the hapten phOX, which when expressed is displayed on the cell surface. Equal concentrations of individual channel and pHook DNA were incubated with 10x concentration of lipofectAce in Modified Eagle's Medium (MEM, Canadian Life

potentials have not been corrected for any junctional potentials that arose between the pipette and bath solution. Data were filtered at 5 to 10 kHz before digitization and stored on a microcomputer for later analysis using the pClamp6 software (Axon Instruments, Foster City, CA). Due to the high level of expression of channel cDNA's in HEK cells, there was no need for signal averaging. The average cell capacitance was quite small, and the absence of ionic current at negative membrane potentials allowed faithful leak subtraction of data.

Data analysis:

The concentration-response curves for changes in peak and steady-state current produced by the test compound were computer-fitted to the Hill equation:

$$f=1-1/[1+(IC50[D])^n] \qquad [1]$$

where f is the fractional current (f=Idrug/Icontrol) at drug concentration [D]; IC50 is the concentration producing half-maximal inhibition and n is the Hill coefficient. The rapid component of inactivation induced by the test compound was much faster than that observed in the absence of drug. Therefore, we used this drug induced time-constant (τ_{block}) as an approximation of the drug channel interaction kinetics, according to the equation:

$$1/\tau_{block} = k_{+1}[D]+ k_{-1} \qquad [2a]$$

and $$Kd=k_{-1}/ k_{+1} \qquad [2b]$$

in which τ_{block} is the current decay time constant caused by the drug; [D] is the concentration of drug; k_{+1} and k_{-1} are the apparent rate constants of binding and unbinding for the drug, respectively. The voltage dependence of block for the uncharged drug was determined as follows: leak-corrected current in the presence of drug was normalized to matching control at each voltage above -20 mV. Using data points in the range of full channel opening ($\geq$ +20 mV), we have calculated the fractional block (f=Idrug/Icontrol) at each potential and fitted data to the Woodhull equation:

respiration was not used and all animals continued to breathe spontaneously throughout the experiment. Blood gas concentrations and blood pH were measured using a blood gas analyser (AVO OPTI I). The femoral artery was cannulated to record blood pressure.

Blood pressure and a modified lead II ECG were recorded using a MACLAB 4S recording system paired with a Macintosh PowerBook (2400c/180). A sampling rate of 1 kHz was used for both signals and all data was archived to a Jazz disc for subsequent analysis.

Vagal nerve stimulation:

Either of the vagi was isolated by blunt dissection and a pair of electrodes inserted into the nerve trunk. The proximal end of the nerve was crushed using a vascular clamp and the nerve was stimulated using square wave pulses at a frequency of 20 Hz with a 1 ms pulse width delivered from the MACLAB stimulator. The voltage (range 2-10V) was adjusted to give the desired bradycardic response. The target bradycardic response was a reduction in heart rate by half. In cases where a sufficient bradycardic response could not be obtained, 10 µg/kg neostigmine iv was administered. This dose of neostigmine was also given after administration of the test drug in cases where the test drug had vagolytic actions.

Test Compounds:

The test compounds were transported to Bogor, Indonesia on dry ice. A near maximum tolerated bolus dose of the test compound, infused (iv) over 1 minute, was used to assess the risk of torsade de pointes caused by each ion channel modulating compound. The actual doses varied slightly depending on the animals weight. Clofilium, 30 µmol/kg, was used as a positive comparison (control) for these studies. The expectation was that a high dose of drug would result in a high incidence of arrhythmias. The test compounds were dissolved in saline immediately before administration.

EXAMPLE 35

ASSESSMENT OF PAIN BLOCKAGE

Guinea pigs were shaved (backs only) and 6 aliquots (50 µl) of compound solution (10 mg/ml) were injected just beneath the skin to form 6 blebs which were outlined with a permanent marker. Pain responses were assessed as above on each bleb at regular intervals up to 4 hours post injection and the duration of pain blockage was recorded for three animals for each test solution.

Table 7

Compound	Duration of Blockage (hours)
1	2.5
2	3
3	2.5
11	3
Saline	0

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually incorporated by reference.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

9. Ion channel modulating compounds according to claim 1 wherein the early repolarising currents comprise the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delay rectifier current (I_{Kur}).

10. Ion channel modulating compounds according to claim 9 wherein the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delay rectifier current (I_{Kur}) comprise at least one of the Kv4.2, Kv4.3, Kv2.1, Kv1.4 and Kv1.5 currents.

11. A composition comprising one or more ion channel modulating compounds according to claim 1 in combination with a pharmaceutically acceptable carrier, excipient or diluent.

12. A compound or composition according to any one of claims 1 or 11 for use in a method for treating or preventing arrhythmia in a warm-blooded animal.

13. A compound or composition according to any one of claims 1 or 11 for use in a method for modulating ion channel activity in a warm-blooded animal.

14. A compound or composition according to any one of claims 1 or 11 for use in a method for modulating ion channel activity *in vitro*.

15. Use of a compound according to claim 1 in a manufacture of a medicament.

16. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective to treat or prevent atrial arrhythmia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

22. A method for inhibiting multiple cardiac ionic currents, comprising administering to a warm-blooded animal in need thereof one or more compounds that either singly or together both block the cardiac ion channels responsible for early repolarising currents and sodium channels, said one or more compounds being administered in an amount effective to block the cardiac sodium ion channels and the cardiac early repolarising ion channels.

23. A method according to claim 22 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

24. A method according to claim 20 wherein one compound blocks both sodium currents and cardiac early repolarising currents from extracellular loci in cardiac cells.

25. A method according to claim 20 wherein each of said one or more compounds has a pKa value of less than 8.

26. A method for treating or preventing a cardiac condition wherein there is an "arrhythmogenic substrate" present in the heart, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together block cardiac early repolarising currents and cardiac sodium currents.

27. A method according to claim 26 wherein said one or more compounds either singly or together both block cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

28. A method according to claim 26 wherein one compound both blocks cardiac early repolarising currents and cardiac sodium currents from extracellular loci in cardiac cells.

36. A method according to claim 34 wherein one compound both blocks cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

37. A method according to claim 34 wherein each of said one or more compounds has a pKa value of less than 8.

38. A method for treating or preventing a cardiac condition wherein there is an increase in acidity of the cardiac milieu from the normal physiological pH of the milieu, comprising administering to a warm-blooded animal in need thereof, an amount effective to treat or prevent said cardiac condition, one or more compounds that either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents.

39. A method according to claim 38 wherein said one or more compounds either singly or together both block cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

40. A method according to claim 38 wherein one compound both blocks cardiac ion channels responsible for early repolarising currents and sodium currents from extracellular loci in cardiac cells.

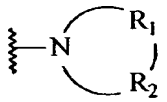
41. A method according to claim 38 wherein each of said one or more compounds has a pKa value of less than 8.

42. A method according to any one of claims 26, 30, 34 or 38 wherein the cardiac condition is ventricular arrhythmia.

43. A method according to any one of claims 26, 30, 34 or 38 wherein the cardiac condition is atrial arrhythmia.

R_1 and R_2 are independently selected from hydrogen, C_1-C_8alkyl, C_3-C_8alkoxyalkyl, C_1-C_8hydroxyalkyl, and C_7-C_{12}aralkyl; or

R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), form a ring denoted by formula (II):



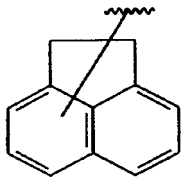
(II)

wherein the ring of formula (II) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1-C_3hydroxyalkyl, oxo, C_2-C_4acyl, C_1-C_3alkyl, C_2-C_4alkylcarboxy, C_1-C_3alkoxy, C_1-C_{20}alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3-C_8carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1-C_6alkyl, C_2-C_4acyl, C_2-C_4hydroxyalkyl and C_3-C_8alkoxyalkyl; or

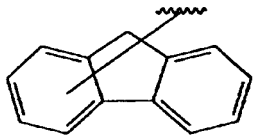
R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring shown in formula (I) at the 3-, 4-, 5- or 6- positions and are independently selected from hydrogen, hydroxy, C_1-C_6alkyl, and C_1-C_6alkoxy, and, when both R_3 and R_4 are attached to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur;

where R_{12} is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl; and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to "X" as shown in formula (I) when Z is CH or N, or Z may be directly bonded to R_{17} when Z is N, and R_{17} is selected from hydrogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl and benzyl;



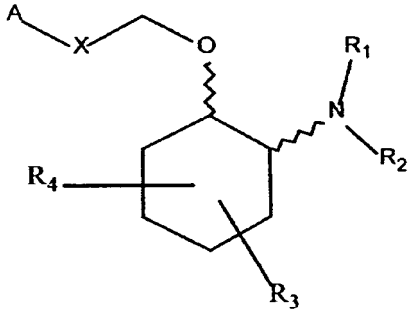
(VII)



(VIII)

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

50. A compound according to claim 49 having formula (IX), or a solvate or pharmaceutically acceptable salt thereof:

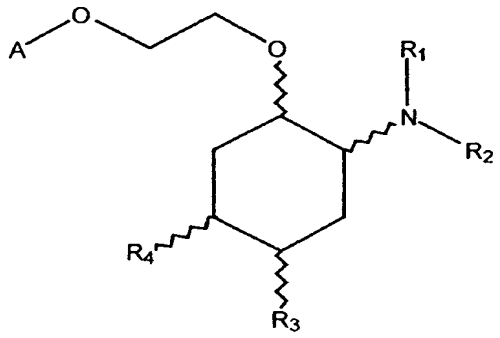


(IX)

wherein, independently at each occurrence,

X is selected from a direct bond, -CH=CH- and $-C(R_6,R_{14})$-Y-;

52. A compound of claim 49 having formula (XI), or a solvate or pharmaceutically acceptable salt thereof:



(XI)

wherein, independently at each occurrence,

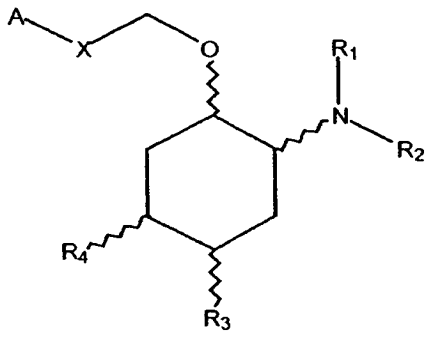
R_1 and R_2 are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5-C_{12}alkyl, C_3-C_8cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as defined in claim 49, wherein Z, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are defined as in claim 49;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

54. A compound of claim 49 having formula (XIII), or a solvate or pharmaceutically acceptable salt thereof:



(XIII)

wherein, independently at each occurrence,

X is selected from a direct bond and -CH=CH-;

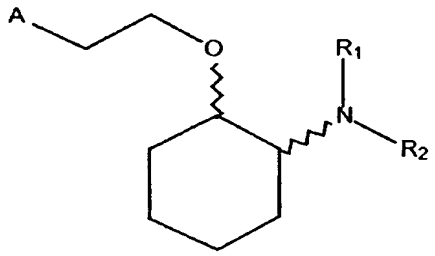
R_1 and R_2 are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_3-C_8cycloalkyl and any of formulae (III), (IV), (V), (VI), (VII) and (VIII) as defined in claim 49, where R_8 and R_9 are defined as in claim 49, R_7, R_{10}, R_{11} and R_{12} are hydrogen, and Z is selected from O, S and N-R_{17} where R_{17} is selected from hydrogen and methyl; with the proviso that A may be selected from formulae (VII) and (VIII) only when X is a direct bond;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

56. A compound of claim 49 having formula (XV), or a solvate or pharmaceutically acceptable salt thereof:



(XV)

wherein, independently at each occurrence,

R_1 and R_2 are defined as in claim 49; and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined in claim 49, wherein R_7, R_{10}, R_{11} and R_{12} are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2, with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

58. A compound, or mixture comprising compounds, selected from the group consisting of:

(+)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;

(+)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;

(+)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;

(-)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;

(+)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;

(-)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;

(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-(3,4-dichlorophenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;

64. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent diseases of the central nervous system in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

65. A method for treating or preventing diseases of the central nervous system in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 64.

66. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent convulsion in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

67. A method for treating or preventing convulsion in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 66.

68. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent epileptic spasms in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

69. A method for treating or preventing epileptic spasms in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 68.

76. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent cystic fibrosis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

77. A method for treating or preventing cystic fibrosis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 76.

78. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent asthma in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

79. A method for treating or preventing asthma in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 78.

80. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent a cough in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

81. A method for treating or preventing a cough in a warm-blooded animal comprising administration of a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 80.

88. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent gastrointestinal disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

89. A method for treating or preventing gastrointestinal disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 88.

90. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent urinary incontinence in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

91. A method for treating or preventing urinary incontinence in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 90.

92. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent irritable bowel syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

93. A method for treating or preventing irritable bowel syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 92.

100. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent long-QT syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

101. A method for treating or preventing long-QT syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 100.

102. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent stroke in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

103. A method for treating or preventing stroke in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 102.

104. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent migraine in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

105. A method for treating or preventing migraine in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 104.

112. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent Becker's myotonia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

113. A method for treating or preventing Becker's myotonia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 112.

114. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent myasthenia gravis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

115. A method for treating or preventing myasthenia gravis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 114.

116. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent paramyotonia congentia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

117. A method for treating or preventing paramyotonia congentia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 116.

124. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent autoimmune disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

125. A method for treating or preventing autoimmune disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 124.

126. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

127. A method for treating or preventing graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 126.

128. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to produce local analgesia or anesthesia in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

129. A method for producing local analgesia or anesthesia in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 128.

136. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent dementia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

137. A method for treating or preventing dementia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 136.

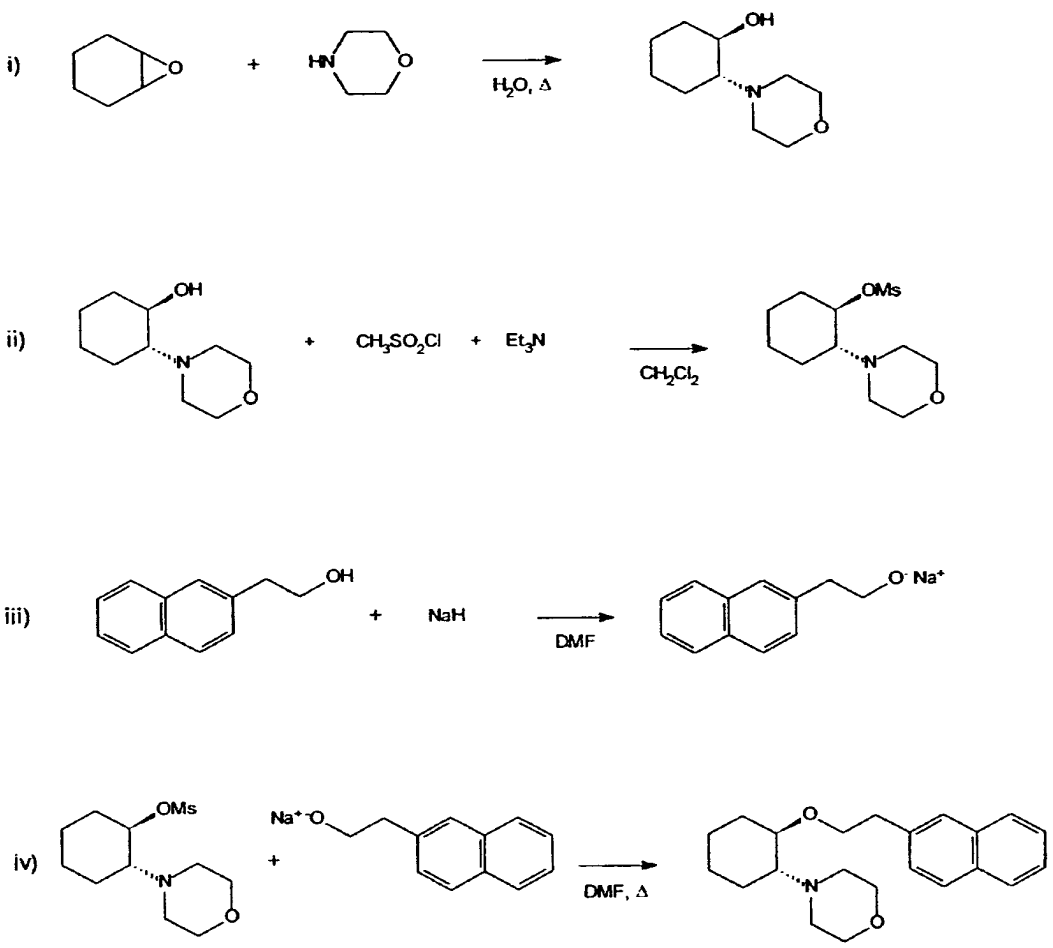
138. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to treat or prevent alopecia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

139. A method for treating or preventing alopecia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to claim 49 or a composition according to claim 138.

140. A pharmaceutical composition comprising an amount of a compound according to claim 49 effective to enhance libido in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

141. A method for enhancing libido in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof an enhancing amount of a compound according to claim 49 or a composition according to claim 140.

142. A compound or composition according to claims 49 or 59 for use in a method for treating or preventing atrial arrhythmia in a warm-blooded animal.


i)
HN
O
H_2O, Δ
OH
N
O
ii)
OH
N
O
+
CH_3SO_2Cl
+
Et_3N
CH_2Cl_2
OMs
N
O
iii)
OH
+
NaH
DMF
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iv)
OMs
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+
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N
O

FIG. 1

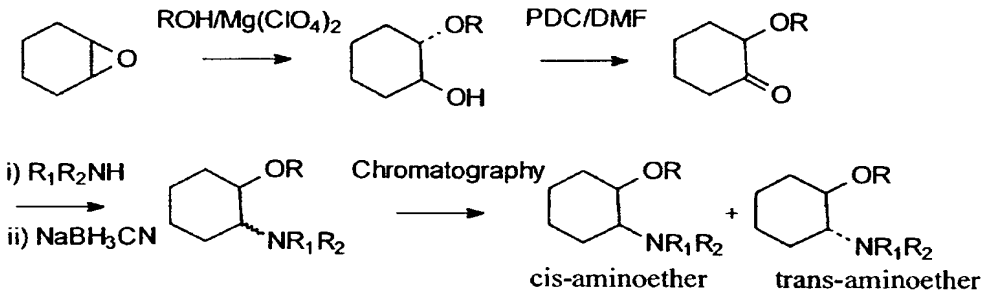
ROH/Mg(ClO4)2
OR
OH
PDC/DMF
OR
O
i) R1R2NH
ii) NaBH3CN
OR
NR1R2
Chromatography
OR
NR1R2
+
OR
NR1R2
cis-aminoether
trans-aminoether

FIG. 3

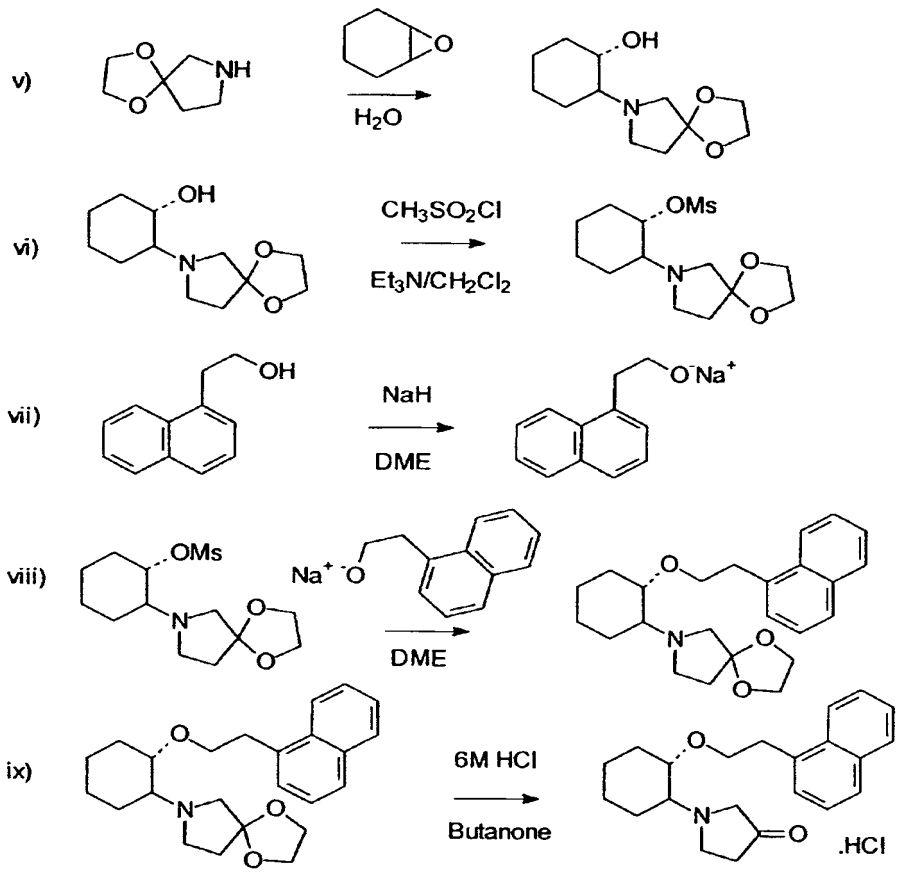
v)
H2O
vi)
CH3SO2Cl
Et3N/CH2Cl2
vii)
NaH
DME
viii)
DME
ix)
6M HCl
Butanone
.HCl

FIG. 4B